

Sesame Seed Food Allergy

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Abstract The number of reports regarding sesame seed food allergy (SFA) has increased significantly worldwide over the past two decades, either due to a genuine increase in SFA or merely an increase in its awareness. Its prevalence is difficult to estimate due to the lack of well designed prospective population-based studies. Based on the available data, we estimate that SFA affects 0.1–0.2 % of the population, in areas where the food is available. Albeit this prevalence appears to be relatively low, it is approximately one-half of that of persistent cow's milk allergy. While only one fatality has been reported, the significant number of SFA patients presenting as anaphylaxis indicates the potential risk. Many reports based the diagnosis of SFA on sensitization criteria alone, particularly amongst atopic dermatitis patients. Elimination of sesame from the diet of these children utilizing such criteria is not justified, and may even increase the risk for developing SFA.

Keywords Food allergy · Sesame seed · SPT · Specific IgE · Oral Challenge · Anaphylaxis

Abbreviations

AD	Atopic dermatitis
DBPCFC	Double blind placebo controlled food challenge
IgE	Immunoglobulin E
OC	Oral challenge
SFA	Sesame-seed food allergy
sIgE	Specific immunoglobulin E
SPT	Skin prick test

Introduction

Food allergy is now recognized as a worldwide medical problem in Westernized countries, and it appears to have increased alongside other atopic disorders, such as atopic dermatitis (AD), allergic rhinitis and asthma [1]. While, in principle, any food may cause an allergic reaction, in practice, the majority of reported food allergic reactions in the pediatric population are caused by only a few food types including cow's milk, eggs, peanuts, soy, fish, wheat, tree nuts, crustaceans and molluscs. Since many children will outgrow their food allergies to soy, eggs, wheat and cow's milk within the first few years of life, the list of the most common food allergens in the adult population is different and comprises peanuts, tree nuts, fish, seafoods and to a lesser extent cow's milk [2–4]. When discussing food allergy it is also important to realize that food allergies differ amongst different communities. This variation indicates that genetic predisposition and environmental influences play major roles in the allergic response [5]. Peanuts, for

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example, are a major allergen in North America and many European countries [3, 4], but are a rare source of allergy in Italy and Singapore [6, 7].

Sesame Food Allergy

Sesame-seed allergy is seen as a growing food allergy of global proportions [8]. In a cross-sectional study of 9,070 children aged 0–2 years, 131 were identified as having food allergy. Sesame was the third most common allergen, preceded only by milk and eggs [9]. Unlike milk and egg allergies, however, tolerance to sesame-seed develops in only 20–30 % of patients [10, 11]. Thus, sesame seed is an allergen of increasing importance and contributes to significant morbidity. Surprisingly, while sesame is already included in the allergens list on both the European Committee and the Canadian Food Inspection Agency, it is still missing from the major food allergens list of the US Food and Drug Administration [8].

The family Pedaliaceae to which sesame belongs contains at least 18 species. Among them, *Sesamum indicum* is widely cultivated in many countries, including India, the Middle East, the United States, China, and other Asian and Latin American countries. Common foods containing sesame seeds are often found in Middle Eastern cuisine, but are gaining popularity now in the US, with the widespread practice of adherence to a "Mediterranean diet". These include snacks such as Halva and salad dressings containing Tahina. In addition, sesame seeds contain approximately 50–60 % oil, and this oil is used not only in the food industries, but also in pharmaceutical and cosmetic products [8, 9].

This review will summarize the literature to date regarding SFA with a special emphasis on its reported prevalence, relationship to atopic dermatitis and reaction severity. As will be evident from our discussion, many of our conclusions are influenced by the mode of diagnosis. Whether there has been an actual increase in the incidence of SFA over the past decade or merely an increase in awareness, SFA clearly is an important issue that should be recognized by physicians.

Prevalence of Sesame Seed Food Allergy

Table 1 is a summary of the reports in the literature regarding SFA. Some of these reports are case descriptions [12–15], while others are results of surveys on food allergy [16–23] or anaphylaxis [24–27]. The differences in study designs make it difficult to draw definitive conclusions regarding SFA but raise interesting questions, such as its prevalence, risk factors for development, relationship to other food allergens, age of onset and rate of recovery, and the potential reciprocal relationship between SFA and atopic dermatitis.

One of the first reports of sesame allergy was reported by Rubinstein in 1950, in a 31-year-old male who experienced anaphylaxis on several consecutive occasions after exposure

to 'halva' and other sesame containing products [12]. Fourteen years later, Torsney reported three patients with sesame food allergy [13], but it was not until 1993 that the first series of nine adult patients with this allergy was reported [14]. Since then, there has been an increasing number of reports covering a wide geographical distribution including Finland, Switzerland, France, Denmark, UK, Italy, Sweden, USA, Canada, Israel, Japan and Australia (see Table 1). Interestingly, while there have been five reports from Israel, there has been only a single report of SFA from the remaining Middle East countries [28], including those countries with reports on food allergy [29, 30].

As mentioned above, it is difficult to obtain an accurate assessment of SFA prevalence in particular, and of food allergies in general. The great variation in estimates relates to the method through which the data was obtained. Some studies base their reports on data collected from perceived food related problems by the patient, whereas others measure actual sensitization to the allergen via SPT, while a few use the gold standard of objective evidence, sensitization (SPT or serum allergen-specific IgE) and an oral food challenge (OFC) [31]. Exacerbating the particular problem of SFA assessment is the paucity of studies attempting to estimate its prevalence. Two studies from Israel estimated the prevalence of SFA as 0.18 % [9] and 0.13 % [32]. The difference in prevalence between these two studies is likely explained by the older age of the latter cohort (4–18 years) versus the former (0–2 years) (see Table 1). These estimates in prevalence are similar to those obtained by self-reported random telephone surveys in the United States with 0.1 % [21] and in Canada with 0.12 % [23]. Higher prevalence rates of between 0.4 [18] and 0.79 % [32] were noted in surveys from the United Kingdom. In the former study, however, only a relatively small number of participants were included, and in only a single case (0.1 %) was clinical allergy demonstrated by an OFC. In the latter study, sesame patients were identified from a questionnaire answered by high school students and by parents on behalf of primary school pupils. There was no validation by any objective criteria, such as SPT or sIgE for the diagnosis of SFA. Furthermore, the population was a selected one, consisting of children attending Jewish schools in the greater London region. A similar prevalence of sesame allergy was reported from Australia at 0.8 % [22]. Although this study was population-based and reportedly OFC proven, the methods utilized raise issues of whether it was overestimated. First, the criterion for a positive SPT was ≥ 1 mm greater than the negative control. Second, patients were considered to be challenge positive if a parent reported urticaria or vomiting within two hours of ingestion of sesame in the past two months at home or even for a subsequent seven days of home-based introduction after a negative challenge in the clinic. Third, patients who had a negative challenge but had symptoms the following day were considered positive [22]. They used

Table 1 Reports on sesame-seed food allergy

N	Country	Age (years) ^a	Number of cases	Allergy (clinical)	Sensitization only	ANA	Mode of diagnosis		Accompanying allergy		Prevalence %	Year/Period ^c	Ref.
							Remote	SPT/sIgE	OFC	AD	Multiple		
1	US	31	1	1	0	1	N	+	+	N	N	1950	[12]
2	US	19–64	3	3	0	3	N	+	ND	NA	NA	1964	[13]
3	US	31–72	4	3	0	2	N	+	ND	NA	NA	1981	[26]
4	Finland	26	1	1	0	1	N	+	+	NA	NA	1991	[15]
5	Swiss	Adult	9	3	0	3	N	+	ND	NA	NA	1978–1991	[14]
6	Australia	Ped	531	NA	NA	NA	N	+	ND	Yes	294/531	1990–1996	[37]
7	France	4–51	9	9	0	5	N	+	+	2/9	4/9	1990–1995	[43]
8	France	Ped	5	NA	NA	NA	N	+	+	NA	NA	1999	[39]
9	Italy	17	1	1	0	1	N	Negative	+	N	N	2000	[24]
10	Israel	5–40 m	10	10	0	0	N	+	NA	10	5	1996–2000	[33]
11	Israel	0–24 m	18	16	2	6	N	+	N	NA	NA	NA	[9]
12	Israel	0.3–29	30 ^c	23	7	6	N	+	Some	13/30	16/23	1998–2002	[33]
13	UK	All	150	150	0	27	Q	ND	ND	63 %	84 %	2002	[16]
14	Denmark	All	NA ^d	NA	NA	NA	NA	NA	NA	NA	NA	2005	[17]
15	UK	6	3	2	1	0	N	+	+	NA	NA	2003–2004	[18]
16	Israel	0.3–54	74	45	29	2	N	+	22	11	70 %	1996–2005	[10]
17	Canada	Ped	101	28	73	NA	N	+	+	Many	Yes	2001–2005	[20]
18	US	0–12 m	1	NA	NA	NA	Q	ND	ND	NA	NA	2005–2007	[41]
19	Israel/UK	4–18	6+31	NA	NA	NA	Q	NA	ND	NA	NA	2004	[32]
20	US	All	13	NA	NA	NA	Q	NA	NA	NA	10/13	2008	[21]
21	US	Ped	70	10	60	0	N	+	NA	NA	Most	2006–2008	[59]
22	Canada	All	4	4	0	0	T	ND	ND	ND	ND	2008–2009	[20]
23	Australia	12 m	88	19	69	0	N	+	+ ^b	NA	NA	2008–2009	[22]
24	Italy	Ped	3	3	0	3	N	NA	ANA	NA	NA	2005–2006	[27]
25	Japan	Ped	91	19	73	NA	N	+	+	NA	NA	2011	[38]
26	Canada	All	5	5	0	NA	Q	NA	NA	NA	NA	2011	[23]
27	Sweden	Ped	5	5	0	5	N	NA	NA	NA	NA	2007	[25]
28	US	Ped	3+7	3+7	0	NA	N	+	NA	NA	NA	2003, 2008	[19]

ANA anaphylaxis, *Ped* pediatric population, *SPT* skin prick test, *sIgE* Specific immunoglobulin E, *OFC* oral food challenge, *US* United States, *UK* United Kingdom, *ND* not done, *NA* not available, *Q* questionnaire, *T* telephone, *N* no

^a Age in years unless otherwise specified

^b See text for details

^c Some of these patients included in [9]

^d Patients with sesame allergy were listed among fruit and vegetables

^e Period is given when available, otherwise year of publication

similar criteria for the estimation of prevalence of egg allergy (8.9 %) (80 % of them tolerated baked egg) and peanut allergy (3 %). These figures are among the highest reported figures for these food groups. It is possible that these diagnostic criteria will set a new standard for the estimation of the prevalence for food allergy. But for the time being the prevalences provided by this study should be considered exceptional. Therefore, it is reasonable to assume that the true prevalence of sesame food allergy is well below 1 % and in the range of 0.1–0.2 %.

Is the Prevalence of Sesame Food Allergy on the Rise?

The wealth of publications on SFA over the past decade gives the impression of a rapid increase in the prevalence of sesame food allergy (Table 1). Indeed, Torsney [13] back in 1964 raised the possibility that the increased consumption of sesame seed in the United States would lead to an increase in SFA prevalence. While the studies were not designed to assess prevalence, no particular increase in prevalence of SFA was appreciated over a 4–5-year time span, even when the data was broken down by geographical locale. As mentioned previously, in Israel, the prevalences reported were 0.18 % in 2000 [9] and 0.13 % in 2004 [32]. However, the latter group consisted of an older age group and thus the data cannot be interpreted as a decline in prevalence over the 4-year period. Another report from a single tertiary care center in the United States showed that among those with a known food allergy, the percentage of patients diagnosed with SFA (2 %) did not increase between 2003 and 2008. This held true despite the fact that the total number of food allergy cases seen at that center had increased well above the increase in the general volume load of allergy and immunology patients [19]. It is reasonable to assume, therefore, that as patients in a region are exposed to a new potential allergen such as sesame, reports will begin to document the presence of the new-found allergy. However, from the available evidence, once introduced into a region, the prevalence of SFA is relatively stable and is likely to range between 0.1 % and 0.2 %.

Sesame Allergy in Israel—Is it a Unique Problem or Just a High Degree of Awareness?

The significant number of SFA reports from Israel [9, 10, 32–34] give the impression that Israel uniquely suffers from a major SFA burden (Table 1). While these studies produced a significant amount of information, they were not population-based and in some the results were limited by the lack of performing OFCs. In the earliest report from Israel, ten infants between the ages of 5 and 41 months old with atopic dermatitis were described [33]. Five of these patients had multiple food allergies and OFCs were not performed to confirm the diagnosis. In 2002, in a large cross-sectional study among

9,070 infants and children aged 0–2 years, sesame allergy was found in 16 cases and was considered to be a major cause of IgE-mediated food allergic reactions in Israel [9]. In fact, sesame was ranked third as an overall cause of food allergy (following the universal allergens—milk and egg) and was second only to cow's milk as a cause of anaphylaxis. The diagnosis was based on a positive SPT and a convincing history of reaction after ingestion. Interestingly, only four cases of peanut allergy were found among the 9,070 infants and children [9]. In a subsequent report from the same group, 23 children with IgE-mediated sesame food allergy and another seven cases of sesame sensitization were reported [33]. Half of the IgE-sesame allergic patients had atopic dermatitis and 70 % were allergic to additional foods as well [34]. In a long-term follow up of 79 patients with positive SPT to sesame, 45 had a convincing history of an allergic reaction to sesame, 11 patients had atopic dermatitis with a positive SPT to sesame and in a third subgroup of 18 patients sensitization to sesame was found incidentally, without any clinical correlation. Among the 45 patients with a convincing history, 16 patients underwent OFC with a positive result in 14. Multiple food allergy was present in more than 70 % of the cases reported in this group as well [10]. Taken together these studies produced a significant amount of information regarding SFA. First, a common thread from these three cohorts from Israel was that SFA was highly associated with AD and multiple food allergies (see Table 1). The studies were not designed, however, to address whether there is a causal relationship between AD and SFA. Second, as described above, SFA does not appear to be more common in Israel as compared to other countries and is unlikely, therefore, to be limited geographically and in severity to Israel. Finally, in the two large cohorts from Israel, the average age of onset was approximately age one year [9] or a median age of one year [10]. A dominant contribution to the early age of onset could be the early exposure to sesame in Israel. It is a common practice among family health centers, nurses, and dieticians to recommend adding Tahini or Halva to the diet of infants in the first year of life as a good source of calories and bio-available iron [10, 34]. A fascinating comparison to peanut allergy would suggest, therefore, that each allergen may have a particular window of opportunity to induce tolerance since early exposure to peanuts is protective against the development of peanut allergy [32]. Alternatively, the prevalence of SFA among Israeli children may be lower than that among Jewish children in England due to the earlier exposure in Israel, similar to peanuts.

Diagnosis

The optimal way to diagnose sesame food allergy would be based on a convincing history accompanied by demonstration of sensitization by SPT or sIgE and confirmed with a DBPCFC

[2]. However, in the real world DBPCFCs are rarely used outside of a research setting and even a simple OFC is not a very common practice [35, 36]. Table 1 presents the total number of patients described in each report and the mode of diagnosis. In some reports, the diagnosis of SFA was based solely on sensitization [37]. In others, in at least some of the cases, it was based on demonstration of sIgE to sesame accompanied by a relatively vague history of a non-immediate skin reaction such as eczema [33, 38, 39]. This method of diagnosis likely contributed to the finding that only 18 of 91 patients that avoided sesame had a reaction during an OFC [38]. While not unique to SFA [40], an important issue is the positive predictive value of SPT and/or sIgE to diagnose SFA. Unfortunately, neither SPT nor sIgE were proven to have a dependable positive predictive value [10, 41–43]. Furthermore, in at least one report, sIgE does not also have an acceptable negative predictive value [10]. The reported negative predictive value of SPT was high in one study [10], lower in another [41] and low with commercial extract and high with raw sesame extract in the third [9]. In contrast, a convincing history of an immediate reaction along with a positive SPT was found to have a positive predictive value in 14 of 16 (88 %) cases [10]. From the above discussion, it seems unjustified to advise the elimination of sesame from a diet of an infant with eczema and a positive SPT or sIgE, unless there is a history of a convincing immediate reaction. In this regard, gradual worsening of atopic dermatitis is not considered a convincing history. In addition, unjustified elimination of sesame from the diet in patients with asymptomatic sensitization, may in fact increase the risk of developing secondary food allergy to sesame as has been described for fish [44] and milk [45].

Clinical Presentation and Natural History

The clinical symptoms of patients with sesame food allergy when evaluated using cohorts defined either by a convincing history and SPT or demonstrated by an OFC, are similar to other IgE-mediated allergic reactions. The majority includes skin manifestations such as urticaria and angioedema and to a lesser extent, gastrointestinal symptoms [9, 10, 34]. In one series, 6/16 (38 %) patients presented with anaphylaxis. Derby et al. reported that 17 % of their sesame allergic patients had suffered potentially life-threatening symptoms [16]. In fact, many of the reports on sesame food allergy were extracted from case reports describing anaphylaxis or from series on anaphylaxis presenting to emergency departments (Table 1). Interestingly, although systemic reactions including anaphylaxis appear to be common, only a single case of death due to an allergic reaction to sesame has been reported [46]. There are at least two convincing reports of sesame-induced anaphylaxis in cases where there was no evidence of sensitization either by SPT or sIgE [10, 43].

Sesame allergy appears to occur in individuals of all ages from infancy to adulthood, including de novo sensitization in adults [8, 9, 16]. An interesting clinical presentation is the non-IgE delayed type hypersensitivity reaction to lignin-like compounds in sesame oil (largely used in the pharmaceutical and cosmetic industries) and clinically expressed as contact dermatitis [8, 47]. Another report drew attention to the growing risk of sensitization to sesame seeds/oil, occasionally as a ‘masked’ allergen [43]. Finally, among the clinical manifestations of sesame allergy is the oral allergy syndrome, manifested by recurrent episodes of wheezing and dyspnea through inhalation [8, 48, 49].

The natural history of SFA appears to be similar to that of peanut allergy [2, 3, 50]. Studies on the natural history of 74 Israeli children with sesame allergy suggested that sesame allergy tends to be persistent, since it resolved in only 20 % of the cohort [10]. Similarly, in a study of 234 children, sesame was the third most common allergen after milk and egg, however, unlike milk and egg allergy, it resolved in only 30 % of the time [11].

Molecular Characterization of Sesame-Seed Allergens

Sesame allergens belong to two broad categories. The first is glycoproteins which have a wide range of molecular mass (7–78 kDa) and the second is lignin-like molecules in sesame oil identified as sesamol, sesamin and sesamol. Until now seven proteins in sesame seeds have been recognized as allergens: Ses i 1 and Ses i 2 [2 S albumin], Ses i 3 [7 S vicilin], Ses i 4 and Ses i 5 [Oleosins], Ses i 6 and Ses i 7 [11 S globulin]. Ses i 3 exhibits 80 % homology with a major peanut allergen (ara h 1) [8, 51–57]. There are reports of cross-reactivity among allergens in sesame and other foods including hazelnut, walnut, rye, kiwi, poppy seed, black walnut, cashew, macadamia, pistachio, and peanuts. However, the clinical significance of this cross-reactivity is unclear [8, 58, 59]. Nevertheless, given that patients with SFA have a high likelihood of having multiple food allergies (mainly peanuts and tree nuts), it would be prudent to test SFA patients for these allergens and to avoid them if clinically indicated.

Treatment and Future Therapies

The only proven effective treatment programs for sesame allergy to date focus on allergen avoidance, concomitant with always having an epinephrine auto-injector available in case of inadvertent exposure. This creates an enormous burden upon these families and the child-care centers they attend to prevent accidental exposure. Furthermore, while there are reports of allergic reactions to sesame seeds that are often found as toppings on various breads and cakes [13, 24], it is our impression that often patients may tolerate the sesame seed but react to sesame-based spreads and sauces

(unpublished observations (YK); confirmed by Hugh A. Sampson, personal communication). Thus, it is important to educate these patients that the ability to eat sesame-topped bread does not imply a tolerance to other sesame-based products.

Given that tolerance to sesame-seed develops in only a minority of patients [10, 11], future research will likely focus on the safety and efficacy of inducing tolerance to sesame by oral immunotherapy. Evidence that the oral introduction of foods can induce tolerance is perhaps best seen in the timing of food administration to young infants. For example, a decreased risk of peanut allergy in Israel appears to be secondary to earlier exposure to peanut protein in Israel (through the ingestion of “Bamba”—a peanut protein coated corn snack) [32]. Furthermore, in a prospective study of over 13,000 infants born at a single medical center, a major risk factor for developing IgE-mediated cow’s milk protein allergy (Type I) was late exposure (continuous) to cow’s milk protein [60]. The common thread between these two studies is that it appears that oral tolerance can be induced through the ingestion of potential allergenic proteins at an early age. The above-mentioned cases deal with the development of complete tolerance and prevention of developing the allergy. Parallel research, however, began to treat patients with known IgE-mediated food allergies with controlled amounts of the allergen until they become desensitized. Currently, with the introduction of oral immunotherapy programs for allergens such as milk [61, 62], egg [63] and peanut [64–66], allergic patients can now freely ingest an allergen that was previously life threatening. To date, no clinical trial has validated this therapeutic approach for IgE-mediated SFA. We are cautiously optimistic, however, that given the growing necessity, the increasing rates of SFA, and the reasonable safety profile of current oral immunotherapy programs, that a trial to desensitize patients allergic to sesame will soon be underway.

Conclusions

Sesame seed food allergy is an increasingly recognized health burden, especially in developed countries. Most cases appear to occur in infancy and early childhood and their clinical presentation includes a significant number of patients with anaphylaxis. Presently, seven proteins in sesame seeds have been recognized as allergens (Ses i 1–7). Furthermore, a significant number of sesame allergic patients are allergic to other foods. The prevalence of sesame allergy is influenced by geographical considerations and environmental exposures. Tolerance to sesame develops in only 20–30 % of patients, highlighting the need for future research to study the safety and efficacy of oral immunotherapy to sesame.

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